

Performance limits of nanobiosensors

P. R. Nair^{a)} and M. A. Alam

School of Electrical and Computer Engineering, Purdue University, West Lafayette, Indiana 47907

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A simple analytical model, based on reaction-diffusion theory, is developed to predict the trade-off between average response (settling) time (t_s) and minimum detectable concentration (ρ_0) for nanobiosensors and nanochemical sensors. The model predicts a scaling relationship $\rho_0 t_s^{M_D} \sim k_D$, where M_D and k_D are dimensionality dependent constants for one, two, and three dimensional nanosensors. We explore the performance limits of nanosensors using this analytical model and support its conclusions using detailed numerical simulation. Our results have obvious and significant implications for analyte density and response time reported in the literature and for design consideration of nanobiosensors and nanochemical sensors. © 2006 American Institute of Physics. [DOI: 10.1063/1.2211310]

A number of research groups have explored the potential of nanoscale sensors for ultrasensitive, label-free detection of biochemical molecules¹⁻⁵ at low analyte concentration in rapid flux. Based on electrostatics considerations, it is well known that two dimensional (2D) cylindrical nanowires are more sensitive to adsorbed charges (e.g., DNA, protein, etc.) compared to one dimensional (1D) planar ion-sensitive field-effect transistor (ISFET) or chemical field-effect transistor (CHEMFET). This classical view of nanosensor response, however, misses the kinetic part of the detection process, i.e., when a sensor is inserted in an analyte field, the time to capture a certain number of analyte molecules (response or settling time t_s) also depends on the dimensionality of the sensor. Therefore, unless $t_{s,2D} \leq t_{s,1D}$ for a given analyte concentration ρ_0 , the nanowire or nanosphere sensors (see Fig. 1), despite their superior electrostatic performance, may actually be impractical for applications that require real time detection of target species at low concentrations.

In this letter, we show that there exist fundamental limits in the concentration of biomolecules which can be detected by any sensor under reasonable settling times in a diffusion limited regime. And this limit is given by the simple scaling relationship,

$$\rho_0 t_s^{M_D} \sim k_D, \quad (1)$$

where M_D and k_D are sensor-dimensionality dependent constants (see Table I). In the following analysis, we explain the reaction-diffusion equation that governs the dynamics of analyte capture, then provide a simple derivation of this scaling relationship (1), and conclude with a discussion of the relevance of this trade-off on nanobiosensors. Finally, we justify the simple derivation of the scaling relationship with detailed numerical simulation.

Consider an isolated sensor immersed in a static analyte solution at time $t=0$ (Fig. 1). The surface of the sensor is functionalized with specific receptors for the target molecules. The rate of conjugation between the target and the receptors is given by

$$\frac{dN}{dt} = k_F(N_0 - N)\rho_s - k_R N, \quad (2a)$$

where N is the density of conjugated receptors, N_0 is the density of receptors on the sensor surface, k_F and k_R are the capture and dissociation constants, and ρ_s is the concentration of analyte particles at the sensor surface at any given time t . The first term of (2a) represents the conjugation between the target and the receptors while the second term denotes the detachment (due to thermal fluctuation, etc.). ρ_s is determined by (2a) as well as by the diffusion of target molecules set by the concentration gradient at the sensor surface which is given by

$$\frac{d\rho}{dt} = D\nabla^2\rho, \quad (2b)$$

where D is the diffusion coefficient of (biological or chemical) target molecules in the solution. The particle flux at the sensor surface is given by

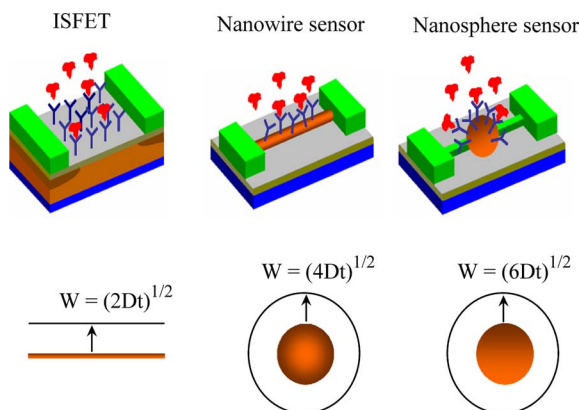


FIG. 1. (Color online) Schematic of a sensor immersed in analyte solution. The diffusion of analyte particles towards a planar device (ISFET) is 1D, towards a cylindrical nanowire surface is 2D, and that to a spherical surface (nanospheres) is 3D. Equilibrium analyte concentration is assumed at a distance W from the sensor surface.

^{a)}Electronic mail: pnair@purdue.edu

TABLE I. Expressions for the dimension dependent parameters used in Eqs. (1) and (6). Here N_s is the minimum number of molecules to be captured for detection, D is the diffusion coefficient of the molecules and a_0 is the radius of nanowires and nanospheres.

	M_D	k_D	A_D	$C_{D,SS}$	$C_{D(t)}$
Planar ISFET	$\frac{1}{2}$	$N_s \sqrt{\frac{2}{D}}$	1	$\frac{D}{W}$	$\frac{D}{\sqrt{2Dt}}$
Cylindrical nanowire	1	$\frac{N_s a_0}{D}$	$2\pi a_0$	$\frac{2\pi D}{\log[(W+a_0)/a_0]}$	$\frac{2\pi D}{\log[(\sqrt{4Dt+a_0})/a_0]}$
Nanosphere	1	$\frac{N_s a_0}{D}$	$4\pi a_0^2$	$\frac{4\pi D}{a_0^{-1}-(W+a_0)^{-1}}$	$\frac{4\pi D}{a_0^{-1}-(\sqrt{4Dt+a_0})^{-1}}$

$$I = D \int_{A_D} \nabla_n \rho ds, \quad (3)$$

where I is the integrated incident flux to the sensor and A_D is the dimension-dependent area of the sensor surface (see Table I). The time response of the sensors as well as the relationship among various sensor parameters [e.g., Eq. (1)] is obtained by solving Eqs. (2) and (3) simultaneously.

Although there is no closed form solution to Eqs. (2) and (3) to analyze the capture dynamics of biomolecules, an excellent approximation to exact solution can be derived by generalizing the approach by Berg.⁶ For large k_F/k_R ($\sim 10^5$ for specific target receptor combinations^{7,8}) and N_0 [$\sim 10^4 \mu\text{m}^{-2}$ (Ref. 9)], Eq. (2a) may be simplified as

$$\frac{dN}{dt} \sim k_F N_0 \rho_s. \quad (4)$$

Based on Ref. 6, the solution of Eq. (2b) in any dimension at steady state is given by

$$I = JA_D = C_{D,SS}(\rho_0 - \rho_s), \quad (5)$$

where $C_{D,SS}$ the diffusion equivalent capacitance (see Table I) and ρ_0 is the equilibrium analyte concentration at a distance W from the sensor surface. The incident flux must balance the (receptor-target) conjugation flux, so that $J = dN/dt$, Eqs. (4) and (5) can be solved to calculate steady state flux to the sensor surface, i.e.,

$$N(t) = \rho_0 t \left(\frac{A_D}{C_{D,SS}} + \frac{1}{k_F N_0} \right)^{-1}. \quad (6a)$$

Equation (6a) predicts that analyte concentration (and therefore the sensor response) grows linearly in time under steady state conditions, as expected.

We can now calculate the transient response of a nanosensor by perturbation of the steady state result in (6a) as follows. We realize that as the forward reaction progresses, the analyte near the sensor surface is depleted as more molecules diffuse to the sensor surface and are captured by the surface receptors. The depletion distance is $W(t) = \sqrt{2nDT}$, where n is the dimensionality of the sensor (see Fig. 1). By assuming quasiequilibrium conditions (to be validated by numerical simulation later), we define a new diffusion equivalent capacitance, $C_D(t)$, as a function of $W(t)$ (last column in Table I) and insert it directly in (6a) to obtain

$$N(t) = \rho_0 t \left(\frac{A_D}{C_D(t)} + \frac{1}{k_F N_0} \right)^{-1}. \quad (6b)$$

Defining the settling time t_s as the time required to capture N_s particles (which corresponds to the minimum amount of detectable signal change), and realizing that the absolute lower limit of t_s is obtained when $k_F \rightarrow \infty$, Eq. (6b) together with the relations given in Table I leads to Eq. (1).

Although the scaling relationship in (1) is simple, it immediately leads to a number of unexpected conclusions. Figure 2 shows the trade-off between settling time and the minimum detectable concentration for planar (1D), cylindrical (2D), and spherical [three dimensional (3D)] nanosensors for a typical DNA detection problem. First, given a reasonable incubation time (~ 100 s), a 1D planar sensor based on ISFET and CHEMFET can detect down to nanomolar levels, while a 2D cylindrical silicon nanowire (SiNW) or carbon nanotube (CNT) sensor ($N_s = 10 \mu\text{m}^{-2}$ corresponds to about two conjugations on a $1 \mu\text{m}$ long, 30 nm radius NW) can detect down to 100 fM concentration. Therefore, the detection limit of a typical 2D nanowire sensors (for the same response time) is three to four orders of magnitude higher compared to planar 1D sensor, justifying the enthusiasm for these novel nanotechnology applications and broadly validating some of the detection estimates published in the literature.^{1-5,11} We believe that this is the first theoretical justification of the plausibility of the measured response time of cylindrical nanosensors reported in the literature. Second, Fig. 2 also shows that although cylindrical nanowire sensor

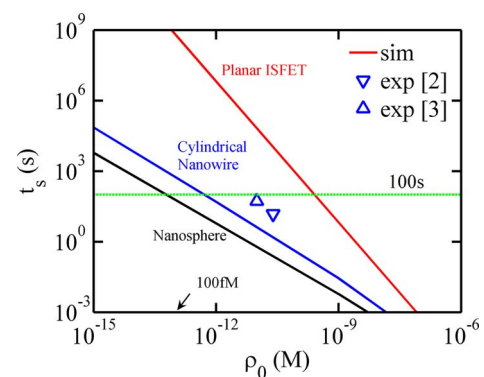


FIG. 2. (Color online) Trade off between the settling time (t_s) and detectable concentration (ρ_0). For a detection time of ~ 100 s, the 2D cylindrical system can detect picomolar concentrations while the planar system can detect only in the nanomolar range [12 base pair (bp) DNA, $D = 4.9 \times 10^{-6} / (\text{bp})^{0.72} \text{ cm}^2/\text{s}$ at 23°C (Ref. 10), $N_s = 10 \mu\text{m}^{-2}$, and $a_0 = 30 \text{ nm}$]. Experimental data (symbols), Refs. 2 and 3, corresponds (approximately) to 2D cylindrical system.

is significantly more sensitive than planar sensor, there is little difference in sensitivity between cylindrical and spherical nanosensors to justify significant new effort in development of nanosphere sensors. Third, it has been conventional wisdom that with proper design and technology development, SiNW- and CNT-based cylindrical sensors should be able to achieve ultrafast detection (<100 s) at femtomolar concentration. Figure 2 shows that this is a challenging target: since $t_{s,2D} \sim 1/\rho_0$, femtomolar detection would require *average* incubation period of hours to days.¹² However, Eq. (1) and Table I allow *a priori* estimates of settling time for sensor geometry and provide specific guidance for design of more sensitive nanobiosensors or nanochemical sensors. This may be achieved by reducing the diameter of the sensor ($a_0 \ll 10$ nm), decreasing the minimum number of analytes required for detectable signals ($N_S \sim 1$) and increasing the effective diffusion coefficient (D) by increasing the ambient solution temperature without exceeding the melting point of the target-analyte conjugate. Since $N_S \sim a_0$ and $\rho_0 \sim a_0^2/D$, scaling the radius of the sensor provides most promising route to femtomolar detection limit with sub-1000-s detection time. However, one must realize that although average detection time can be reduced to <100 s for small diameter sensors, statistical variability can still be significant and must be accounted for during sensor array design. Finally, once a sensor has been calibrated for a biomolecule of known diffusion coefficient, Eq. (1) can be used for electrical determination of diffusion constants of unknown biomolecules based on the geometry of the sensor and the average response time t_s .

Finally, we provide numerical validation of the scaling law in Eq. (1). The numerical solution to Eqs. (2) and (3) shows that the sensor response evolves in three phases (see Fig. 3). Phase 1 is reaction limited and occurs at very short time as the sensors begin to capture the analyte particles available very close to the surface and the response for planar, cylindrical, and spherical systems vary linearly with time. Once the region near the surface is depleted of DNA strands, the diffusion-limited transport of DNA through water molecules dictates sensor response (phase II) which varies as $\sim t^{1/2}$ for a 1D planar sensor and $\sim t^1$ for cylindrical and spherical sensors. Finally, in phase III, the response of the sensor saturates due to the detailed balance of forward and backward reactions [Eq. (2a)]. Given typical dimensions of nanosensor, DNA length, operating temperature, etc., one would typically observe phase II within the measurement window. Excellent match between numerical solution and analytical model [Eq. (6b)] validates the scaling relationship in Eq. (1). Although we showed comparison only for a single

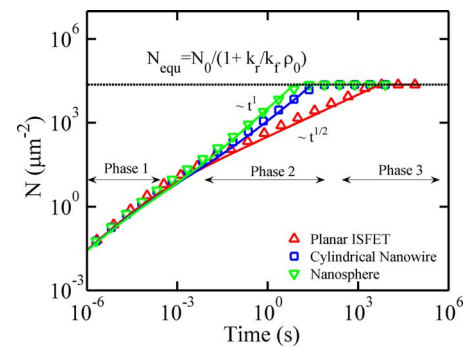


FIG. 3. (Color online) Sensor response for a constant supply system—comparison between analytical results [Eq. (6b)] and numerical simulation. The solid lines indicate analytical results while the symbols indicate numerical simulations (bp=20, $N_0=10^5 \mu\text{m}^{-2}$, $a_0=1 \mu\text{m}$, $k_f=3 \times 10^6/\text{M s}$, and $k_r=1$).

system, this excellent agreement between simulation and analytical results has been shown to be valid for wide range of practical operating conditions and device parameters.

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- ¹¹DNA detection using rectangular silicon nanowires was reported in Refs. 2 and 3. The time response of a rectangular NW is slightly slower than a 2D cylindrical NW of comparable radius. Cylindrical nanowires used in simulations have the same surface area as the rectangular nanowire devices used in Refs. 2 and 3 (width \times height $\sim 50 \times 50 \text{ nm}^2$).
- ¹²DNA detection in femtomolar concentrations, reported in Ref. 1, was done using an ac signal. Due to the associated ac electrokinetic effects Ref. 13, the response may not be dominated by diffusion. Still the reported detection time (~ 100 s for 10–100 fM) is in the broad range predicted by Eq. (1).
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